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DEPARTMENT OF THE ARMY
Fort Detrick
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INTERFERENCE OF THE NEUROTROPIC STRAIN OF RIFT VALLEY FEVER VIRUS WITH THE PANTROPIC STRAIN IN MICE

Comptes Rendus de la Societe de Biologie
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Pages 1634-1638

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Yasuo Saburi

We showed in a preceding report[1] that the neurotropic strain of Rift Valley virus multiplies in the liver and spleen of mice after intraperitoneal injection. However, the peak of virulence of a suspension of these organs was not as high as in the case of the pantropic strain. It is possible that all the cells of the mouse susceptible to the pantropic strain are equally capable of producing the neurotropic strain, but in small quantities, or only a small fraction of the cells produces the virus. We undertook experiments to determine whether the neurotropic strain interferes with infection by the pantropic strain in mice. The results are set forth below.

The materials and procedure were described in our previous report[1] with the exception of the pantropic strain, which was obtained from the Pasteur Institute in Paris in 1938.

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* M. Matumoto, I. Nishi, and Y. Saburi, C. R. Soc. Biol., 1958, Vol. 152, p. 1623.

The virus was used in the form of serum from infected mice taken shortly before they died. The pantropic strain was titrated by intraperitoneal injection of mice with 0.1 ml of the material.

1. Inhibitory effect of the neurotropic strain on infection of mice by the pantropic strain. Mice were inoculated intracerebrally with the neurotropic virus. The brains were removed in the agonal state to make a 33% suspension. The pantropic strain in the form of serum from infected mice was serially diluted with brain suspension. The mixture thus contained the undiluted neurotropic strain and the pantropic strain serially diluted. In the control mixtures, the suspension of infected brains was replaced with that from new mice. Mice were injected intraperitoneally with 0.21 ml of the mixtures. One group of mice received only the neurotropic strain. The doses of the neurotropic strain were equal to $10^{7.60}$ and $10^{7.93}$ times the LD_{50} for experiments 1 and 2. The inoculated mice were kept under observation for 14 days. The results are shown in the figure.

Injection of the mixture of neurotropic and pantropic viruses

1 - Treatment with the neurotropic virus

2 - Treatment with noninfected brain (control)

3 - Time after incoulation (in days)

4 - Dilution of the pantropic virus

5 - Interval between inoculation and death of the animals

6 - Summary of the results of experiment 1

7 - Summary of the results of experiment 2

8 - Injection of the neurotropic virus used in experiment 2.

No injection of the pantropic virus

There was a marked delay in the death of the animals and a decrease in the death rate. Both phenomena could be ascribed to the inhibitory effect of the neurotropic virus on infection by the pantropic virus.

2. Appearance of neutralizing antibodies in the circulating blood after inoculation of the neurotropic virus. In order to determine whether neutralizing antibodies interfere with the inhibitory action of the neurotropic virus against infection by the pantropic virus, it would be useful to know how long the antibodies remain in the blood after injection of the neurotropic

virus. This information was obtained from the experiments reported in our earlier article.[1] In these experiments 0.1 ml of a 33% emulsion of brains infected by the neurotropic virus was injected intraperitoneally. The mice were exsanguinated at different intervals. The serum collected from 5 mice was used for the assay.

Table 1

Appearance of Neutralizing Antibodies in the Blood after Injection of the Neurotropic Virus

1 - Intervals after inoculation
2 - day(s)
3 - Neutralization index

Neutralizing antibodies were found in the circulating blood 3 or 4 days after injection of the virus. This fact implied that the neutralizing antibodies do not interfere with the inhibition under study and led us to believe that the inhibition is due to inferference.

3. Influence of the mode of inoculation on the effect of interference. We injected intraperitoneally 4 groups of 8 mice each with 0.2 ml of a 33% emulsion of brains infected by the neurotropic virus. The controls were injected with an emulsion of noninfected brains. The inoculation dose was equal to $10^{8.60}$ times the LD_{50}. Two hours later the pantropic virus was injected intraperitoneally, subcutaneously, intravenously, or intracerebrally. The LD_{50} of the pantropic virus used was $10^{-9.17}$ X 0.1 ml by intraperitoneal injection, $10^{-9.50}$ X 0.1 ml or less by intravenous injection, and $10^{-9.50}$ X 0.025 ml or less by intracerebral injection. In another experiment, the mice were injected with neurotropic virus subcutaneously instead of intraperitoneally. The dose was equal to $10^{8.26}$ times the LD_{50}. The LD_{50} of the pantropic virus used was $10^{-9.17}$. The results are presented in Table II.

The results indicate that intraperitoneal inoculation of the neurotropic virus can interfere with infection by the pentropic virus regardless of the mode of injection and that subcutaneous inoculation of the neurotropic virus does not interfere with the

pantropic virus whatever the method of inoculation except the subcutaneous.

Table II

Influence of the Mode of Injection on the Inhibitory Effect

1 - Neurotropic virus

2 - Pantropic virus

3 - Number of days of survival

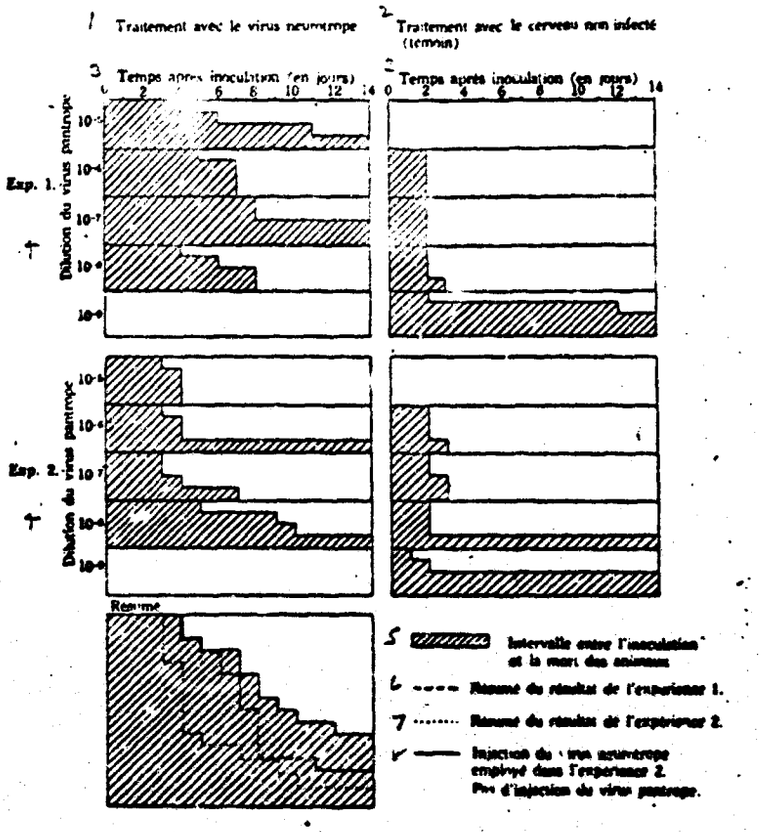
4 - Noninfected brain (control)

5 - Number of days until death

6 - ∞ : Mice surviving

Summary

The infection of mice with the pantropic strain of Rift Valley virus can be inhibited by an intraperitoneal injection of the neurotropic strain. The neutralizing antibodies do not appear until [illegible] 3 or 4 days after injection of the neurotropic strain and they would not interfere with the present inhibition. The neurotropic strain injected intraperitoneally interfered with the pantropic strain regardless of the [illegible] in which the pantropic virus was injected. Injected subcutaneously, the neurotropic strain interfered only with the pantropic strain injected subcutaneously.



injection du mélange des virus neurotrope et pantrope.

Intervalles après inoculation		1 jour	2 jours	3 jours	4 jours	5 jours	6 jours	7 jours
3 Indice de neutralisation	Exp. 1	—0,33		>1,67			2,34	
	Exp. 2	0,54		1,34		2,00		4,34
	Exp. 3	0,00	0,33	0,00	2,00	2,00		2,00

Tableau I. — Apparition dans le sang d'anticorps neutralisants après l'injection du virus neurotrope.

Exp. 1

1 Virus neurotrope	ip. 0,2 ml			
2 Virus pantrope	ip. 0,1 ml	s.c. 0,1 ml	iv. 0,1 ml	ic. 0,025 ml
3 Jours de survie	5 (*)	5	2	3
	5	5	5	4
	5	7	5	4
	6	7	7	4
	6	7	7	5
	7	7	7	5
	7	7	8	5
	∞	∞	14	7
4 Cerveau non-infecté (témoin)	ip. 0,2 ml			
5 Jours de survie	2	2	2	2
	2	2	2	2
	2	2	2	2
	2	2	2	2
	2	2	2	2
	2	3	2	2
	2	3	2	2
	2	3	2	2

Exp. 2

1 Virus neurotrope	ip. 0,2 ml	s.c. 0,2 ml				s.c. 0,2 ml
2 Virus pantrope	ip. 0,1 ml	ip. 0,1 ml	iv. 0,1 ml	s.c. 0,1 ml	ic. 0,025 ml	—
3 Jours de survie	5	2	2	2	2	3
	5	2	2	2	2	5
	5	2	2	2	2	6
	6	2	2	2	2	∞
	12	2	2	3	2	∞
	∞	2	2	3	2	∞
	∞	2	2	13	2	∞
	∞	2	2	14	2	∞
4 Cerveau non-infecté (témoin)	ip. 0,2 ml	s.c. 0,2 ml				
5 Jours de survie	2	2	2	2	2	
	2	2	2	2	2	
	2	2	2	2	2	
	2	2	2	2	2	
	2	2	2	2	2	
	2	2	2	2	2	
	2	2	3	2	2	
	2	2	3	2	2	

(*) Nombres de jours jusqu'à la mort. ∞ : Souris ayant survécu.

Tableau II. — Influence de la voie d'injection sur l'effet inhibiteur.